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# Migraineurs show a high prevalence of antiphospholipid antibodies.

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**Keywords:** anti-beta2 glycoprotein antibodies, anticardiolipin antibodies, antiphospholipids, aura, lupus anticoagulant, migraine.

## Summary.

**Background:** It has been observed that migraineurs show a higher risk of thrombosis and that the most frequent symptom reported by patients with antiphospholipid syndrome is headache, especially migraine. **Objectives:** The aim of our research was to evaluate the prevalence of antiphospholipid antibodies (aPL) in a random cohort of migraineurs. **Patients/Methods:** This analytic, comparative case study was performed to evaluate the prevalence of antiphospholipid antibodies by comparing a population of migraineurs with and without aura with sex- and age-matched controls. Both the diagnosis of migraine and the laboratory diagnosis of aPL positivity were made on the basis of the most recent international guidelines. **Results:** Between September 2008 and August 2009, we recruited 284 consecutive patients (225 women and 59 men, 203 without aura and 81 with aura) and 225 controls (174 women and 51 men). Positivity for at least one test for aPL (LAC, ACA IgG or antiβ2GPI IgG) was detected and confirmed in 12% (n = 33) of patients and in 3% (n = 7) of controls (odds ratio, 4.08; confidence interval, 1.77–9.39; P = 0.0004). Two of the patients had triple positivity for aPL (LAC, ACA and antiβ2GPI) and one had double positivity (LAC and antiβ2GPI); none of the controls showed multiple positivity. **Conclusions:** Our data show that migraineurs have a significantly higher prevalence of antiphospholipid antibodies, and point towards the fact that the two conditions may be comorbid or even that migraine may be an early sign for identifying patients with aPL positivity.

## Introduction

Migraine is the most frequent type of primary headache, and is characterized by severe, predominantly unilateral throbbing pain associated with phonophobia, photophobia, nausea and vomiting [1]. Various diseases are believed to be comorbid with migraine, and in recent years particular attention has been paid to the vascular complications of migraine. Furthermore, a significantly increased risk of stroke and cerebrovascular lesions has also been documented [2–4]. In the 1980s, Hughes and colleagues first described the antiphospholipid syndrome (APS) [5], and headache and migraine are currently included among the symptoms [6]. There are several studies that have looked for a correlation between migraine and antiphospholipid antibodies (aPL), but so far data on the prevalence of antiphospholipid antibodies and any possible relationship with migraine are conflicting and incomplete, with a prevalence ranging from 0% to 30% of patients [7–19]. Recent data drawn from the European Registry for APS revealed that the most frequent symptom in APS is headache, mostly classified as migraine with and without aura [20,21]. More recent data taken from the Euro-Phospholipid Project confirmed a 20% prevalence of migraine in patients with APS [22]. It was therefore hypothesized that APS may be the link between migraine and stroke, and recommendations were made to search for aPL in patients suffering from migraines or from recurrent headaches [23]. None of the existing studies based on current guidelines for the diagnosis of migraine or for the laboratory diagnosis of APL is large enough to evaluate the possible correlation between migraine and aPL. This is even more important because headache is not presently among the diagnostic criteria for APS. We therefore designed this single-center, laboratory blinded, analytic comparative case study to assess the prevalence of aPL in patients with migraine.

## Patients and methods

### Patients

Patients were enrolled between 1 September 2008 and 31 August 2009. We compared two groups: the first group included patients with migraine who were consecutively visited at our Headache Center, and who routinely underwent blood chemistry examinations for comorbidity. The second was a control group made up of volunteers who did not suffer from headache, and included employees of our hospital who volunteered to participate in the study while undergoing their routine annual blood test for occupational medicine. The inclusion criterion for patients was migraine, as diagnosed according to the International Classification of Headache Disorders criteria [1]; exclusion criteria included the presence of other types of headache and the use of anticoagulation therapy. Exclusion criteria for controls were the presence of headache and/or the use of anticoagulants. Patients and controls were sex and age matched ( $\pm 5$  years). The severity of headache was estimated using an index of severity (defined as the sum of the severity of each day of headache per month). Severity was defined as: 1 = mild pain that does not need therapy and is not disabling; 2 = moderate intensity of pain, disabling, requiring therapy, well manageable with treatment; 3 = very severe pain, severely disabling, requiring therapy, poorly responsive to symptomatic drugs). The patients were all seen by a neurologist who is experienced in headache diagnosis, and a "computer-assisted" history was drawn up. The same information on medical history was collected from the control subjects by means of a questionnaire.

### Laboratory methods

All patients and controls were evaluated for blood cell count, partial thromboplastin time (PTT), prothrombin time (PT), lupus anticoagulant (LAC), anticardiolipin antibodies (ACA), and antibodies to beta 2 glycoprotein (Ab2G). The laboratory methods we used included the coagulation method (Roche Diagnostics, Stago, France), Stage Rack: LA-PTT lupus anticoagulant, confirm test, ratio of basal and mix with pool of sera LAC SCT, SCT confirm test, SCT normalized ratio, LAC Russell "Viper Venom (DRVVT) and DRVVT confirm ratio) for LAC. We used microtiter IEMA (Aesku Diagnostics, Wendelsheim, Germany); AESKULISA Cardiolipin IgG and IgM) for ACA, and microtiter IEMA (Aesku Diagnostics; AESKULISA  $\beta 2$  Glycoprotein IgG and IgM) for Ab2G.

### Sampling procedure

Sampling was carried out with minimal stasis, using the Vacutainer system. We used 4.5 mL tubes containing sodium citrate 0.109 mol/L (3.2%) as the anticoagulant for LAC. Plasma was separated from the corpuscular phase within 3 h of collection by double centrifugation at 1800 g (15 min for each spin). The lack of platelets in plasma was confirmed by counting performed with the Sysmex SE 2100 system, and the search for the LAC was performed every day within 5 h of collection using STA-R Roche equipment. Test tubes without anticoagulant and with gel separator were used for the detection of ACA and Ab2G on blood that was drawn at the same time as samples for LAC testing, using the Vacutainer system. The test tubes were centrifuged within 2 h of collection (time varying between 30 min and 2 h) and the serum was kept in the original tube with the plug in place, in the refrigerator at 4–8 °C, and examined within 7 days of collection. Tests were performed by the Triturus analyzer, made by GRIFOLS (Parets del Valle's, Barcelona, Spain).

### Positivity criteria

Patients having at least two confirmed positive test results at intervals of > 12 weeks were considered positive. The tests were considered positive if LAC positivity of any strength was observed with at least two out of three (PTT-LA, SCT, DRVVT) positive tests (low positivity = ratio 1.20–1.50, moderate positivity = ratio 1.50–1.80, high positivity = ratio > 1.80); ACA IgG or Ab2G IgG were considered positive if IgG was > 40 (moderate positivity = IgG 40–80, high positivity = IgG > 80). With regard to positivity criteria, we followed both the international criteria for the diagnosis of APS [6], as well as the latest recommendations stating that only medium-high titers of IgG, Ab2G or ACA should be considered positive [24]. Our hospital laboratory regularly undergoes regional quality controls carried out by the Regional Consortium for APS.

**Sample size** We estimated a likely prevalence of aPL among controls of 1–5%. We then calculated that in order to detect any significant differences between the two groups, using Delta 10%, 5% alpha error, beta error 90% and the two-tailed test, we would have to recruit between 136 and 206 subjects per cohort.

### Statistical analysis

Analysis of variance for groups was performed using the SAS system for PCs. Data were adjusted for sex using the Cochran–Mantel–Haenszel statistics, and then stratified by sex. We used odds ratio (OR) (confidence interval [CI] 95%) as a measure of statistical significance. The study was carried out in collaboration with the University of Turin, Master's course for rare diseases. All the necessary authorizations were obtained. Patients and controls provided informed consent allowing the use of personal, clinical and instrumental data.

## Results

In 1 year, 284 patients (225 women and 59 men) and 225 controls (174 women and 51 men) were recruited. The mean age of the patients was 39 years, on average 5 years younger than the controls. Among migraineurs, 203 suffered from migraine without aura (M) and 81 had migraine with aura (MA). Average age at onset of headache was 18 years, while the frequency of the attacks was 9 days month<sup>-1</sup> and the index of severity was 20. These data were similar in subgroups of migraineurs with and without aura. Table 1 shows the details. Positivity for aPL was confirmed in 12% of patients (n = 33) and in 3% (n = 7) of the controls (OR, 4.08; CI, 1.77–9.39; P = 0.0004). Table 2 shows the details. Positivity for LAC was confirmed in nine patients (six patients, ratio < 1.50; three patients, ratio > 1.80) but in none of the controls (OR, 8.52; CI, 1.07–67.41; P = 0.006). ACA positivity was similar in the two groups (four patients with moderate IgG titer and one control with high IgG titer). Regarding the positivity for Ab2G, it was significantly higher in migraineurs (OR 3.51 (CI 1.41–8.71) P = 0.004), both in the subgroup of migraine without aura (OR, 3.99; CI, 1.33–11.93; P = 0.008) and the subgroup of migraine with aura (OR, 3.28; CI, 1.26– 8.52; P = 0.01) (11 patients with moderate IgG positivity, 14 patients with high IgG positivity, two controls with moderate positivity and four controls with high positivity). After stratification by sex, statistical significance still remained for women in general, and for migraine without aura. Two of the patients (one male and one female) were positive for LAC, ACA and Ab2G, and one patient (a female) was positive for LAC and Ab2G, while none of the controls had multiple positivity. Subgroup analysis on the basis of age at onset, frequency of monthly headache and headache severity index showed a significantly higher prevalence of aPL positivity in all categories, as well as a trend towards higher positivity among migraineurs suffering from greater frequency and more severe forms (see Table 3 for details). We also evaluated patients and control subjects for other possible diseases, and were able to rule out inflammatory connective tissue disorders.

## Discussion

To our knowledge, ours is the first cohort study carried out on a large population of migraine patients who were studied using shared criteria, on the basis of current guidelines for both the neurological diagnosis of migraine [1] and the laboratory diagnosis for aPLs [5,24]. Comparing our data with those of previous studies is difficult because the populations and diagnostic and laboratory parameters are heterogeneous. The study by Avcin et al. [9] is the only one that investigated both ACA and Ab2G with welldefined laboratory criteria, sampling methods and parameters of antibody positivity, and that used the International Classification to evaluate migraine. The authors studied a small population of children with migraine, using two control groups, one consisting of children with tension headache and the other of healthy children. These same authors repeated the laboratory tests over time and confirmed positivity at any titer for IgM or IgG ACA or Ab2G in about 16% of children in each group, but positive medium-titer was only confirmed in two migraine patients (5%) over time. Our study, which was conducted on an adult population, revealed a confirmed-over-time positivity at any titer in approximately 17% of patients compared with 4% of controls (data not shown). This percentage is similar to what was found in the population studied by Avcin et al. [9], whereas confirmed positivity in the medium-high titers was observed in 12% of our patients. All other published works only involved studies on ACA [8–19], while LAC was only mentioned in three older works that described the first case reports or selected neurological patients [7,8,19]. The tests for aPL were repeated over time in only three cases to confirm results [13,18,19] and included comparisons between patients and controls [10–13,15,17]. On average, few patients were studied in those works and the results that were obtained vary broadly (from 0% to 37%). No differences were detected between the various subtypes of migraine, nor was any relationship observed between aPL and migraine with aura [10,12,15,17–19]. Furthermore, among migraineurs, we found a 4% prevalence of APS syndrome (eight vascular APS and four obstetric APS), compared with 0.4% of controls (one case of vascular APS). Although the study of these data is not among the objectives of this study, they may suggest a possible correlation between migraine and aPL as well as one between migraine and APS. Whether there is a link between migraine and aPLs, and what that link might be is not clear. They may be genetically related, but both are heterogeneous and multifactorial diseases, and no specific causative gene has yet been identified [25–27]. They share the same male-female distribution [28–39], and furthermore, a possible common pathogenetic basis might be platelet activation and similar serotonergic involvement [31–36]. We must also take into consideration that complement activation is common in both migraine [37–39] and APS [40–42]. Migraine is not considered a clinical criterion for the diagnosis of antiphospholipid antibody syndrome, even in the presence of elevated levels of plasma aPLs. Such patients are defined as “confirmed asymptomatic aPL positive” as they do not have documented thrombotic vascular events. However, we believe that on the basis of our data and on those that are emerging from the European Registry [21,22], the current exclusion of migraine from among the diagnostic criteria should be reconsidered.

## Conclusion

Our study is the first to demonstrate a higher prevalence of aPL positivity in migraineurs compared with controls by means of a large analytical comparative population study. This study involved appropriate selection of patients and

controls, and strict application of criteria for laboratory research, for the definition of aPL positivity, and for the clinical definition of migraine. It is not clear what the link between migraine and aPL is. Our data point towards the fact that the two conditions may be comorbid. Further studies applying clinical and laboratory diagnostic criteria both for migraine and for the assessment of aPL are needed to confirm our data. Additional work is also required to assess whether any active therapy for hemostasis may be advantageous even for migraine prophylaxis.

### Addendum

C. Cavestro designed and conducted the study, and wrote the protocol and the final report. G. Micca and F. Molinari performed the hematologic tests. M. Bazzan contributed to analysis of data, evaluation of patients and tests, and co-wrote the final report. R. Aloj, R. Iannini and E. Pedemonte contributed to patient and control recruitment. C. Di Pietrantonj was responsible for data analysis and statistical testing. M.C. Frigeri followed all legal declaims and monitored the conduction of the study. D. Roccatello was the external supervisor and consultant. All authors contributed to the preparation of the final report.

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### Disclosure of Conflict of Interests

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**Table 1** General characteristics of the recruited population

	Migraineurs			Controls
	Total	M	MA	
Number of subjects	284	203	81	225
Men	59	38	21	51
Women	225	165	60	174
Age (mean $\pm$ SD)		39 ( $\pm$ 13)	38 ( $\pm$ 14)	44 ( $\pm$ 8)*
Patient's age < 20	35	24	11	—
21–40	110	79	31	76
41–60	128	93	35	148
> 60	11	7	4	1
Age at headache onset (mean $\pm$ SD)		17 ( $\pm$ 9)	18 ( $\pm$ 7)	
Headache frequency in days month <sup>-1</sup> (mean $\pm$ SD)		10 ( $\pm$ 8)	8 ( $\pm$ 8)	
Headache severity index (mean $\pm$ SD)		21 ( $\pm$ 17)	18 ( $\pm$ 17)	

M, migraine without aura; MA, migraine with aura; SD, standard deviation. \*Scheffe test by age,  $P < 0001$ .

**Table 2** APL positivity in patients; whole sample and by subgroups

Sex adjusted	Migraine	OR	CI	P	Migraine without aura	OR	CI	P	Migraine with aura	OR	CI	P	Controls
Confirmed positivity													
Total	33	4.08	1.77–9.39	0.0004	23	3.93	1.65–9.36	0.0010	10	4.32	1.59–11.76	0.002	7
Men	9	9.00	1.1–73.70	0.0156	4	5.88	0.63–54.94	0.0826	5	15.63	1.7–143.81	0.0023	1
Women	24	3.34	1.34–8.37	0.0067	19	3.64	1.42–9.37	0.0045	5	2.55	0.75–8.67	0.1232	6
Confirmed LAC positivity													
Total*	9	8.52	1.07–67.41	0.0060	7	9.93	1.22–80.61	0.0030	2	8.14	0.83–79.84	0.0210	0
Men*	4	8.35	0.44–158.96	0.0582	3	10.15	0.51–202.72	0.0412	1	7.54	0.29–192.68	0.1166	0
Women*	5	8.71	0.48–158.50	0.0478	4	9.72	0.52–182.04	0.0388	1	8.80	0.35–218.91	0.0879	0
Confirmed ACA positivity													
Total	4	3.21	0.36–28.35	0.2640	3	3.31	0.35–31.29	0.2630	1	2.76	0.16–46.71	0.4730	1
Men*	2	4.48	0.21–95.47	0.1845	1	4.12	0.16–103.96	0.2440	1	7.54	0.29–192.68	0.1166	0
Women	2	1.55	0.14–17.25	0.7187	2	2.12	0.19–23.63	0.5311	0	0.96	0.04–23.78	0.5562	1
Confirmed AB2G positivity													
Total	25	3.51	1.41–8.71	0.0040	17	3.28	1.26–8.52	0.0100	8	3.99	1.33–11.93	0.0080	6
Men	5	4.63	0.52–41.01	0.1336	2	2.78	0.24–31.82	0.3932	3	8.33	0.81–85.34	0.0380	1
Women	20	3.30	1.21–8.97	0.0139	15	3.38	1.20–9.52	0.0152	5	3.07	0.86–11.01	0.0714	5

OR, odds ratio, controls vs. patients, sex adjusted and stratified by sex. Sex adjusted using the Cochran–Mantel–Haenszel test, migraineurs vs. controls, and stratified by sex. \*Sex adjusted with Logic test, correction of 0.5 in zero-cell.

**Table 3** Analysis of patients stratified by age at onset, headache frequency and headache severity, compared with controls

	aPL positive	aPL negative	Significance
Age at headache onset			
1–18 years	22	167	OR 4.10 (CI 1.71–9.83) $P$ 0.0007
> 18 years	11	81	OR 4.23 (CI 1.59–11.28) $P$ 0.0020
Headache frequency (days month <sup>-1</sup> )			
1–4 days	15	95	OR 4.92 (CI 1.94–12.45) $P$ 0.0003
5–15 days	9	107	OR 2.62 (CI 0.95–7.22) $P$ 0.0545
> 15 days	9	49	OR 5.72 (CI 2.03–16.11) $P$ 0.0003
Headache severity*			
0–12	17	124	OR 4.27 (CI 1.72–10.58) $P$ 0.0008
13–45	12	102	OR 3.66 (CI 1.40–9.58) $P$ 0.0050
> 45	4	25	OR 4.98 (CI 1.36–18.22) $P$ 0.0078
Controls	7	218	—

\*Headache Severity Index: sum of the severity of each day of headache, defining the severity as 1 = mild pain that does not need therapy and not disabling, 2 = moderate intensity of pain, disabling, requiring therapy, well manageable with treatment, 3 = very severe pain, severely disabling, requiring therapy, poorly responsive to symptomatic drugs.